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Date: May 28, 2008 Rebecca A. Bellas

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application

Applicant:	Bevec	Art Unit:	1654
Serial No.:	10/564,849	Examiner:	Christina Bradley
Filed:	Jan. 13, 2006		

Title: BIOLOGICALLY ACTIVE SUBSTANCE OF A VASOACTIVE INTESTINAL PEPTIDE FOR TREATING INTERSTITIAL LUNG DISEASES

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

I, Dr. Dorian Bevec, declare and say as follows:

I am the inventor of the claims of the above-identified patent application. I hold a Ph.D. from the University of Munich and habilitation from the University of Vienna. I have gained ten years of experience with Novartis in Vienna and two years with the biotech company Axxima in Martinsried, Germany. I have been employed by

Mondobiotech since 2001 as Chief Scientific Officer. I have been involved in various research projects associated with treatment of interstitial lung infections for 7 years.

The relationship between inhibition of dendritic cell maturation and treatment of idiopathic pulmonary disease, hypersensitive pneumonia and diffused panbronchitis is a result that is explicitly suggested by the relevant scientific literature and, hence, expected by persons having ordinary skill in the art. The relationship between dendritic cell inhibition and treatment of the stated pulmonary diseases has been explored in the scientific literature. It is common in the art to utilize screening methods employing tissue cultures to identify active substances that have a high likelihood of exhibiting similar activity in whole organisms. CD83 is one of the best known markers of human dendritic cell maturation; persons skilled in the art recognize CD83 expression as a proxy for the level of dendritic cell maturation. As such, assays demonstrating a reduction in CD83 activity are highly predictive of utility in treating disease states where the importance of mature dendritic cells is known. Further, the assay method employing human dendritic cells disclosed in the Application is an *in vivo* assay method, where the assay monitoring CD83 expression is performed using living human dendritic cells.

Marchal-Somme et al (Exhibit 1) disclose the formation of organised lymphoid tissue in the lung of idiopathic pulmonary fibrosis (IPF) patients and the importance of dendritic cells in these aggregates of lymphoid tissue. This lymphoid tissue contains mature dendritic cells expressing CD83, CD86 and CD40; however, such mature dendritic cells were virtually absent in healthy lungs (see page 5736, col. 2, lines 11 to 14). Further, T lymphocyte aggregates infiltrated by mature dendritic cells were observed in fibrotic lungs and there was a positive correlation between the numbers of dendritic cells per square millimetre and the intensity of lymphocyte infiltration (see page 5736, col. 2, lines 16 to 19). The T lymphocytes also expressed CD28, the receptor for CD86 costimulatory molecules expressed by mature dendritic cells (see page 5736, col. 2, last two lines to page 5737, col. 2, first two lines). Based on the data presented in this paper, the authors conclude that memory T cells accumulating in IPF

lesions due to dendritic cells maturing locally play a central role in sustaining chronic inflammation (see page 5738, col. 1, lines 12 to 14) and that the observed organised lymphoid structure can persist in an autonomous fashion by recruiting maturing dendritic cells and recently activated T cells, and thus chronically sustain inflammation in the absence of local lymphocyte proliferation (see page 5738, col. 1, lines 24 to 28). The authors suggest that the presence of these organised lymphoid structures comprising dendritic cells could explain why anti-inflammatory drugs are mostly ineffective in the treatment of IPF, as these agents have poor activity against dendritic cells and suggest that mature dendritic cells should be a therapeutic target (see page 5738, col. 2, lines 2 to 11).

Marchal-Somme et al clearly supports mature dendritic cells as being a critical element in chronic inflation caused by pulmonary fibrosis. That is, mature dendritic cells expressing CD83 recruit T lymphocytes expressing complementary CD28 receptors, wherein recruitment of T lymphocytes causes the inflammatory immune reaction. Therefore, inhibition of dendritic cell maturation is expected to ameliorate chronic inflammation in interstitial lung diseases, such as idiopathic pulmonary fibrosis, hypersensitive pneumonia and diffused panbronchiolitis.

Todate et al (Exhibit 2) discloses the importance of dendritic cells in the lungs of diffuse panbronchiolitis patients. In a study of bronchiolar tissue from the lungs of diffuse panbronchiolitis patients, it was found that the number of CD83 expressing dendritic cells was significantly higher in diffuse panbronchiolitis patients than in normal control patients (see page 150, col. lines 10 to 12). Specifically, there was a marked increase of CD83 expressing dendritic cells in the submucosal tissue in comparison to control subjects (see page 150, col. 1, last 3 lines to col. 2, first line and column 2, line 5 to 9). The authors conclude that the marked accumulation of CD83 expressing dendritic cells in the submucosal tissues could result in effective stimulation of submucosal infiltrating T lymphocyte cells by the their powerful antigen presenting capacity (see page 152, col. 1, lines 57 to 61). That is, Todate et al also recognizes the

critical role of mature dendritic cells expressing CD83 as the cause of chronic inflammation.

Thus, it is clear from these publications that mature dendritic cells play a central role in the pathogenesis of interstitial lung diseases, such as idiopathic pulmonary fibrosis, hypersensitive pneumonia and diffused panbronchiolitis. However, neither of these publications suggest that a peptide comprising SEQ ID NO: 4 would be useful to inhibit the maturation of dendritic cells. The data presented in the Application, as filed, clearly demonstrates the inhibitory effect of the claimed peptides on the maturation of dendritic cells. In order to make and use the invention of Claim 1, a clinician merely has to administer a peptide comprising SEQ ID NO: 4 through an appropriate means. No undue experimentation is required to select a peptide that has utility; all sequences containing SEQ ID NO: 4 are expected to have some level of inhibitory effect on maturation of dendritic cells. No undue experimentation is required to match a specific peptide containing SEQ ID NO: 4 to utility for treatment of a specific disease, since Idiopathic pulmonary fibrosis, hypersensitive pneumonia, and diffused panbronchiolitis are all conditions that are linked to maturation of dendritic cells.

In addition, the subsequent data presented below demonstrates the inhibitory effect of the claimed peptide on further markers of mature dendritic cells.

IN VIVO DATA

The following *in vivo* human data demonstrating the beneficial modifying effects of the claimed peptide SEQ ID NO: 1 in the course of treatment of pulmonary fibrosis was obtained from macrophages and dendritic cells from bronchoalveolar lavages from patients after 4 weeks of inhaled treatment:

- A decrease of TGF-β1, on average by -30.7%
- A decrease in CD83 %, on average by -30.6%,
- A decrease in CD40 %, on average by -9.2%,

- A decrease in HLA-DR, on average by -6.9%
- A decrease in CD86 %, on average by -15.9%,

Further the following *in vitro* human data demonstrating the beneficial effect of the claimed peptide for the treatment of idiopathic pulmonary fibrosis, hypersensitive pneumonia or diffuse panbronchiolitis have been obtained:

The claimed peptide SEQ ID NO: 1 inhibited in a tested range from 10^{-5} M to 10^{-8} M the TGF-β - induced expression of alpha-smooth muscle actin on cultured human fibroblasts. This is one of the key modes of activity in the field of interstitial lung diseases, as this effect prevents the physical transformation from regular fibroblasts into so-called myofibroblasts. Myofibroblasts are regarded as one of the most important indicators in terms of increasing the severity of idiopathic pulmonary fibrosis, hypersensitive pneumonia or diffuse panbronchiolitis.

The importance of CD 83, CD40 and CD86 expressing dendritic cells in the pathogenesis of idiopathic pulmonary fibrosis, hypersensitive pneumonia or diffuse panbronchiolitis is discussed above in relation to the Marchal-Somme el al (Exhibit 1) and Todate et al (Exhibit 2) publications.

Also of particular importance is the finding regarding decrease of TGF-β1 of on average by -30.7%. One current hypothesis for the cause of idiopathic pulmonary fibrosis, hypersensitive pneumonia or diffuse panbronchiolitis suggests that an unknown repeated stimulus produces acute lung injuries involving alveolar epithelial cells and the destruction of subepithelial basement membranes. These areas are then characterized by the breakdown of type IV collagen and laminin and the invasion of interstitial collagens type I and III.

Alveolar epithelial cell injury and basement membrane disruption leads to local recruitment, differentiation, and proliferation of fibroblasts. Soluble mediators secreted by alveolar epithelial cells in the surrounding milieu stimulate fibroblast activity. Of these mediators, TGF-β1 has probably become the most important one, due to its strong activity to stimulate mesenchymal growth and its ability to modulate cellular immune functions. TGF-β1 is known to cause severe pulmonary fibrosis when

overexpressed in animal models, and a significant overexpression of this mediator is found in human idiopathic pulmonary fibrosis, hypersensitive pneumonia or diffuse panbronchiolitis. TGF-β1 inhibits interferon gamma-dependent beneficial immune reactions.

Recruitment and proliferation of fibroblasts are critical events in the pathogenesis of idiopathic pulmonary fibrosis, hypersensitive pneumonia or diffuse panbronchiolitis. Following epithelial cell injury, fibroblasts migrate and proliferate into the alveolar septae and spaces. Areas of rapidly proliferating myofibroblasts and fibroblasts situated adjacent to sites of epithelial cell and basal membrane damage are the primary sites of ongoing injury and repair. The combination of excessive production and deposition of extracellular matrix (ECM) proteins and reduced proteolysis of ECM contributes to the fibrotic process in idiopathic pulmonary fibrosis. ECM proteins (e.g., tenascin, fibronectin, and collagen) are overexpressed in idiopathic pulmonary fibrosis, hypersensitive pneumonia or diffuse panbronchiolitis. Activation and proliferation of fibroblasts amplifies the fibrotic process and in idiopathic pulmonary fibrosis, hypersensitive pneumonia or diffuse panbronchiolitis fibroblasts proliferate at enhanced rates, even in the absence of external signals.

The claimed peptide SEQ ID NO: 1 has been shown to inhibit the maturation of dendritic cells and a mediator of fibroblast proliferation, which as discussed above are central to the pathogenesis of idiopathic pulmonary fibrosis, hypersensitive pneumonia or diffuse panbronchiolitis, thus the significant effect of the claimed peptide for the use in the treatment of idiopathic pulmonary fibrosis, hypersensitive pneumonia or diffuse panbronchiolitis is clearly proven.

I, Dorian Bevec, hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued therein.

Dorian Bevec, Ph.D.

May 26, 2008

Date